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Effect of environmental factors on the development of allergic disorders in infancy

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A total of 1167 infants were followed for 1 year in a population-based prospective study to assess the effect of environmental factors on the development of allergic disorders. Some of these environmental factors are interdependent. Mothers who formula fed their infants smoked more often ($p < 0.001$) and tended to belong to lower social classes ($p < 0.01$). Logistic regression analysis was performed to adjust for these confounding variables. Maternal smoking adversely affected the prevalence of asthma ($p = 0.003$), allergic rhinitis, and episodes of wheezing and total allergy ($p = 0.02$). Infants in lower socioeconomic groups developed asthma significantly more often ($p = 0.03$) than infants born in higher socioeconomic groups. There was a nonsignificant trend for infants born in summer to develop asthma more than infants born in winter ($p = 0.08$). No effect of these factors was observed on eczema, food intolerance, or on the subgroup of infants with definite allergy (clinical disorder with positive skin prick test [SPT]). Exposure to animal dander did not influence the prevalence of clinical disorder, but positive SPT reaction to cat dander was more prevalent in infants who were exposed to cats and/or dogs ($p = 0.04$). Positive SPT to house dust mite occurred significantly more often in infants who were formula fed ($p = 0.05$). The environmental factors had a profound effect on the prevalence of asthma but not on other allergic disorders. (*J ALLERGY CLIN IMMUNOL* 1992;90:235-41.)

Key words: Environmental factors, maternal smoking, season of birth, asthma, allergic disorders

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Received for publication Oct. 1, 1991.
Revised April 6, 1992.
Accepted for publication April 7, 1992.
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1/1/38533

The interplay of genetic and environmental factors in the development of allergic disorders remains a subject for extensive investigation. The possibility of manipulating environmental factors to prevent the development of allergy attracts attention. Factors encountered in infancy may be of special importance.¹ Since the pioneer study of Grulee and Sanford,² there have been numerous studies of the protective effect

of breast-feeding with conflicting results.³ The effect of passive smoking^{4,5} and month of birth^{6,7} have also been investigated. The aim of this study on infants born consecutively during a period of 14 months was to study the effect of method of feeding, passive smoking, season of birth, presence of pets, and social class on the prevalence of allergic manifestations in infancy.

MATERIAL AND METHODS

The parents of 1215 infants born in the Isle of Wight between January 1989 and February 1990 were contacted soon after the birth of their child to participate in a prospective study to determine the influence of genetic and environmental factors on the development of allergic symptoms in infancy. Data on the influence of family history of atopy, cord IgE level, and pets on allergic disorders have been published separately.^{8,9} The study was fully explained and informed consent was obtained. Approval for the study was given by the local ethical committee. Forty-two parents moved from the island during the first year and six families declined to attend follow-up appointment. This analysis is based on data from 1167 infants.

Family history

Information was obtained on the history of atopic disorders in the immediate family. A diagnosis of asthma, eczema, and allergic rhinitis was accepted when diagnosis had been made and treated by a doctor. The infant was regarded as having a positive family history when either parent or sibling suffered from one or more atopic disorder. Allergy in distant relatives was not considered.

Parental smoking

Information was obtained on the parental smoking habits separately for mother and father. Parents who smoked regularly (one or more cigarettes a day) were regarded as smokers. Occasional smoking (less than one cigarette per day) was disregarded.

Pets

Information was also obtained on the presence or absence of pets in the house.

All infants were observed regularly by health visitors (registered nurses with postgraduate training) up to the age of 1 year. The health visitors recorded feeding history and details of any medical problem. Any infant with a history suggestive of allergic disorder was examined by Dr. Arshad, and SPTs were performed with allergen extracts (Soluprick, ALK Laboratories, Copenhagen, Denmark) against timothy-grass pollen, cat dander, and HDM in every infant. These three allergens were selected since >90% of atopic adults would react to one or more of these allergens. Additional SPTs were performed if the history suggested the tests. A wheal of the same size as the wheal to histamine response (1 mg/ml) was regarded as + + +, and half that size, + +. Flare alone was ignored; + + or more was considered positive. Allergic disorders were defined as follows:

Abbreviations used

SPT:	Skin prick test
HDM:	House dust mite
S-E:	Socioeconomic
OR:	Odds ratio
CL:	Confidence limit

Asthma: three or more separate episodes of cough and wheezing

Eczema: chronic or chronically relapsing, itchy dermatitis (lasting more than 6 weeks) with characteristic morphology (areas of scaly, erythematous, and pruritic lesions) and distribution (face, postauricular area, scalp, extensor surface of extremities, and flexural creases)

Rhinitis: recurrent nasal discharge or blockage with attacks of sneezing and itchy eyes

Food reactions: a history of vomiting, diarrhea, colic, or rash within 4 hours of ingestion of a particular food on at least two occasions

Definite allergy: one or more disorders as defined above with positive SPT

Hospital records were scrutinized on all infants who were hospitalized during the first year for additional information.

Infants breast-fed exclusively for 3 months were classified as breast-fed, and the remainder were classified as formula-fed. Information on pets and tobacco smoking within the house was updated at 1 year on all infants.

S-E class

Data on the occupation of father and mother were obtained from hospital maternity notes. The infants were classified by the father's occupation; the mother's occupation was coded if she was a single parent or if her husband was unemployed and she was employed. The social classes were formed according to the Registrar General's classification: class 1, professionals (doctors, solicitors and directors); class 2, farmers, managers, teachers, engineers, etc.; class 3, skilled workers, such as nurses and technicians; class 4, low-skilled workers, such as factory workers; class 5 (a), unskilled workers, such as laborer; and class 5 (b), unemployed.

To highlight the effect of S-E class, analysis was performed with classes 1, 2, and 3 grouped together as higher S-E group (professional and skilled workers) and classes 4 and 5 (semiskilled, unskilled, and unemployed) grouped together as lower S-E group.

Season of birth

To analyze the effect of season of birth, infants were classified into four groups according to month of birth. Infants born in December, January, and February were defined as winter births. Infants born in March, April, and May were defined as spring births. Infants born in June, July, and August defined as summer births, and infants born

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TABLE I. Effect of various environmental factors on the development of allergic disorders in infancy

	Total	Definite	Asthma	Eczema	Rhinitis	Food reactions
Method of feeding						
Formula (N = 747)	22.6	6.3	12.0*	9.9	2.9	6.3
Breast (N = 420)	22.1	6.4	6.7	11.9	3.8	8.0
Maternal smoking						
Smoking (N = 281)	27.0*	6.0	17.8†	11.4	2.8	9.3
No smoking (N = 886)	21.0	6.4	7.8	10.5	3.4	6.2
Season of birth						
Summer (N = 273)	27.1	7.7‡	14.7*	12.8	4.8‡	8.4
Winter (N = 353)	19.5	3.4	7.4	11.3	1.7	5.4
S-E Group						
Lower (N = 385)	23.4	6.5	13.5*	11.8	3.6	8.1
Higher (N = 323)	21.4	9.0	6.5	12.1	3.7	7.4
Cats and/or dogs						
Yes (N = 601)	21.6	6.2	9.0	9.3	3.0	6.5
No (N = 566)	23.3	6.5	11.5	12.4	3.5	7.6

All figures are percentages.

* $p < 0.01$.† $p < 0.001$ (χ^2 test with Yates's correction).‡ $p < 0.05$.

in September, October, and November defined as autumn births.

Statistical methods

Chi-square test with Yate's correction was used for the detection of difference between proportions. Logistic regression analysis was used to obtain the independent contribution of factors to the risk of allergic disorders. With asthma as the dependent variable, all risk factors of interest were included in the model, and significance was tested for each one, controlling for all other factors by means of the likelihood ratio test. Adjusted ORs with 95% confidence intervals were calculated. With total and definite allergy as the dependent variable, a stepwise procedure was used to build the model with a cutoff of $p = 0.05$ used to determine entry into the model. Statistical analyses were performed with SPSS/PC + V4 (SPSS, Inc., Chicago, Ill.).

RESULTS

The percentage of infants with allergic manifestations according to various risk factors is presented in Table I. Breast-feeding offered some protection against asthma ($p < 0.01$). Asthma was more common in infants whose mothers smoked ($p < 0.001$). Infants born in the summer months (June, July, and August) suffered from asthma more frequently ($p < 0.01$) than infants born in winter months (December, January, and February). A higher proportion of infants belonging to the lower S-E group suffered from asthma ($p < 0.01$) but not other allergic disorders. No difference in any allergic disorder could

be demonstrated between children with or without pets (cats and/or dogs) at 1 year.

Three hundred forty-four infants were referred to the clinic by the health visitors, and all infants were skin tested. The percentage of infants with skin reactivity at 1 year to common inhalant and food allergens for each risk factor is presented in Table II. Reaction to HDM occurred significantly more often ($p = 0.05$) in infants who were formula-fed and in infants exposed to maternal smoking. A significantly higher proportion of infants whose mothers did not smoke demonstrated positive reaction to egg ($p = 0.05$). Reaction to cat dander was more prevalent in infants who were exposed to cats or dogs ($p = 0.05$).

Some of these environmental factors are interrelated. There were highly significant differences in smoking habit and S-E class between groups of mothers who chose to breast-feed and those who formula-fed (Table III). Moreover, in the higher S-E group, only 14% of the mothers smoked compared with 31.4% in the lower S-E group ($p < 0.001$). The prevalence of maternal asthma was similar in various subgroups (Table III). Because of these confounding variables, the net effect of the factors may not be as is outlined in Tables II and III. The logistic regression model was used to obtain the adjusted ORs for each factor. The baseline for each factor was defined as method of feeding, breast-feeding; smoking, no maternal smoking; S-E groups, higher S-E group; season of birth, winter births; pets, no cats or dogs; maternal

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TABLE II. Effect of environmental factors on skin test reactivity to common inhalant and food allergens

	GP	HDM	Cat	Dog	Egg	Cow's milk	Others*
Method of feeding							
Formula (N = 222)	1.4	7.7 [†]	5.0	1.4	9	3.2	2.7
Breast (N = 122)	2.5	0.8	4.1	1.6	9.8	5.7	3.3
Maternal smoking							
Smoking (N = 90)	1.1	10 [†]	6.7	2.2	3.3	2.2	2.2
No smoking (N = 254)	2.0	3.5	3.9	1.2	11.4 [†]	4.7	3.1
Season of birth							
Summer (N = 100)	2.0	5.0	5.0	1.0	7.0	4.0	5.0
Winter (N = 89)	0	4.5	4.5	1.1	6.7	2.2	1.1
S-E group							
Lower (N = 123)	0.8	5.7	2.4	1.6	8.9	1.6	4.9
Higher (N = 93)	5.4	5.4	9.7	1.1	12.9	6.5	4.3
Cats and/or dogs							
Yes (N = 165)	0.6	4.9	7.3 [†]	1.2	8.5	4.8	3.6
No (N = 179)	2.8	5.6	2.2	1.7	10.1	3.4	2.2

GP, Grass pollen.

All figures are percentages.

*Include tree pollen, budgie, wheat, peanut, strawberry, and fish.

[†] $p < 0.05$ (χ^2 test with Yates's correction).

asthma, mother did not have asthma; sex, female; SPT, negative.

Unfortunately, entries of parent's occupation were incomplete in the maternity notes, and these data were available for only 708 infants. However, infants in which S-E class was known were compared with infants in which it was not known for various confounding variables (Table III). There were no significant differences.

The predominant effect of environmental factors was on the development of asthmatic symptoms. Logistic regression was performed with asthma as the dependent variable, including all factors of interest ($n = 708$). Maternal smoking, lower S-E group, maternal asthma, and male sex were significant risk factors (Table IV).

Formula-feeding and summer birth failed to reach statistical significance when they were adjusted for other confounding variables in the model. When maternal smoking was included as a separate factor, it was not significant (OR = 0.91; CL = 0.4 to 1.86) and had no effect on the significance of other factors.

When S-E group was excluded from the model so that all 1167 infants can be used, summer birth (OR, 2.13; CL, 1.25 to 3.66; $p = 0.006$) and formula-feeding (OR, 1.62; CL, 1.02 to 2.77; $p = 0.04$) became significant. The statistical significance of maternal smoking, maternal asthma, and male sex was also increased ($p < 0.001$ in each case).

Twenty-seven percent of infants with asthma had skin test positive to one or more allergens. Skin test sensitivity might have an effect on the relationship of

asthma to various risk factors. To adjust for this, SPT was added to the next regression model (Table V). All data were available on 210 infants. Maternal smoking and S-E group remained significant risk factors.

The influence of risk factors on the prevalence of total allergy (infants with one or more allergic disorder) and definite allergy (subgroup with positive skin tests to one or more allergens) was analyzed with a stepwise procedure. With regard to total allergy, maternal smoking (OR, 1.64; CL, 1.10 to 2.45; $p = 0.02$) and maternal asthma (OR, 2.71; CL, 1.66 to 4.44; $p < 0.001$) were the only significant factors. Summer birth ($p = 0.06$) and sex ($p = 0.06$) just failed to reach statistical significance. Only maternal asthma was significantly related to infants with definite allergy (OR, 2.82; CL, 1.44 to 5.54; $p = 0.005$).

With positive skin test to HDM and cat as the dependent variable, logistic regression was performed to test the significance of method of feeding, maternal smoking, S-E group, month of birth, and presence of cat or dog in 344 infants in which skin tests were done. For skin test sensitivity to HDM, formula-feeding was the significant risk factor (OR, 8.04; CL, 0.98 to 67.11; $p = 0.05$). Presence of cats or dogs in the house was a risk factor for skin test sensitivity to cat dander (OR, 3.29; CL, 1.04 to 10.46; $p = 0.04$).

DISCUSSION

Allergic symptoms are extremely common during the first year of life. Symptoms do not always represent IgE-mediated type I allergy. Adverse food re-

TABLE III. The relationship of various confounding variables to method of feeding, maternal asthma, and known/unknown social class

	Formula (N = 747)	Breast (N = 420)	Mat asthma (N = 122)	No mat asthma (N = 1045)	SC known (N = 708)	SC not known (N = 459)
Sex	357 (47.8%)	220 (52.4%)	60 (49.2%)	517 (49.5%)	338 (47.7%)	239 (52%)
Pos FH	424 (56.8%)	236 (56.2%)	—	—	390 (55%)	270 (58.8%)
Mat asthma	78 (10.4%)	44 (10.5%)	—	—	79 (11.2%)	43 (9.4%)
Smoking mothers	232 (31.1%)	49* (11.6%)	30 (24.6%)	251 (24%)	167 (23.6%)	114 (24.8%)
Lower S-E group	261 (59.5%)	124† (46.1%)	42 (53.2%)	343 (54.5%)	—	—
Formula feeding	—	—	—	—	439 (62%)	308 (67%)

Mat, Maternal; SC, socioeconomic class; Pos FH, positive family history of atopy.

* $p < 0.001$ (χ^2 test with Yates's correction).† $p < 0.01$.

TABLE IV. Effect of various risk factors on the development of asthma in infancy (N = 708)

Risk factors	OR	95% CI	Significance
Formula feeding	1.65	0.91-2.99	0.09
Maternal smoking	2.30	1.34-3.92	0.003
Lower S-E group	1.84	1.05-3.20	0.03
Season of birth			
Autumn	1.33	0.56-3.17	0.52
Spring	0.83	0.35-1.94	0.66
Summer	1.97	0.91-4.25	0.08
Cats and dogs	0.69	0.42-1.17	0.16
Maternal asthma	2.45	1.29-4.78	0.01
Sex			
M	1.80	1.08-3.01	0.02

TABLE V. Effect of various risk factors on the development of asthma in infancy (after adding SPT as an independent variable; N = 210)

Risk factors	OR	95% CI	Significance
Formula feeding	1.77	0.88-3.56	0.11
Maternal smoking	2.89		0.003
Lower S-E group	2.45	1.21-4.88	0.01
Season of birth			
Autumn	0.77	0.27-2.23	0.63
Spring	0.71	0.25-2.02	0.52
Summer	1.33	0.51-3.43	0.56
Cats and dogs	0.94	0.49-1.80	0.86
Maternal asthma	1.49	0.67-3.33	0.33
Sex			
M	1.56	0.81-3.04	0.18
Positive SPT	3.20	1.55-6.58	0.002

actions, infantile eczema, and rhinitis could all have different immunologic mechanisms. A subgroup of infants with definite allergy was defined whose symptoms were backed by relevant positive SPTs. In infancy, bronchial hyperactivity is revealed by recurrent cough and wheeze, usually after a viral respiratory tract infection. It has been termed wheezy bronchitis, infantile wheezing, pseudoasthma, or asthma. There is controversy in the literature as to the nature and outcome of recurrent wheezing in infancy.¹⁰ A longitudinal study by Williams and McNicol¹¹ concluded that wheezing in response to viral infections and asthma has the same underlying basic disorder. Park et al.¹² found that 87% of infants who wheezed during the first year did not have asthma at the age of 10 years, although they were more likely to have asthma with increasing number of wheezy attacks during the

first year. We preferred to use the term asthma for wheezy infants, since there was strong genetic component in this group (significant relation to maternal asthma and male sex).

This finding is not to imply that most of these infants will continue to wheeze or that they are necessarily atopic. Indeed, evidence for atopy (positive SPT) was found in only 27% of infants with recurrent wheezing during the first year.

The environmental factors studied in this cohort were method of feeding, passive smoking, social class, season of birth, and exposure to pets. The first three risk factors are closely related, and any individual effect would have to be adjusted for these and other possible variables, such as maternal asthma and

sex of the infant. None of the environmental factors had any significant effect on eczema, rhinitis, or food intolerance (Table I). The effect on "total allergy" was primarily due to the effect on prevalence of asthma.

In line with several previous studies,¹³⁻¹⁵ we could not detect an association between mode of feeding and incidence of total allergy. Some studies have found a protective effect of breast-feeding on wheezing.^{16, 17} Since there are so many interrelated confounding variables, these must be taken into account when the effect of method of feeding on the development of allergic disorders is being assessed. In this study, there appeared to be a protective effect of breast-feeding against wheezing episodes, but when adjustment was made for other variables, this effect became nonsignificant. It is believed that breast-feeding provides immunologic protection against infections with transfer of IgA and IgG through breast milk. If infantile wheezing is a nonspecific response to viral infections, it was surprising that no significant effect of breast-feeding was observed. There was an association between sensitivity to HDM and formula-feeding. No firm conclusions could be drawn on the relationship to skin test sensitivity because the only infants who were skin tested were infants who demonstrated symptoms and who had been referred to the clinic by health visitors. This possible association needs confirmation.

Passive smoking is known to increase bronchial responsiveness and symptoms in children with asthma.¹⁸ Parental smoking, particularly maternal smoking, increases the risk of respiratory illness during the first year of life.¹⁹⁻²¹ We found a significant effect of maternal smoking on wheezing in infants. Paternal smoking was not a risk factor, presumably because the father does not usually smoke in the vicinity of the infant for sufficiently long periods. It is unlikely that parents misled us about their smoking habits since information on smoking, as well as the presence of pets, was checked by the health visitors who visit homes frequently after the birth of a baby.

Recently, Murray and Morrison²² reported that children with atopic dermatitis are at a greater risk of developing asthma if the mother smokes. It was believed that atopic dermatitis signified a predisposition to atopy, whereas smoking acts as an adjuvant factor. In this cohort, the effect of maternal smoking was independent of hereditary factors, such as maternal asthma or sex of the infant and skin test sensitivity of the infant. From these data, maternal smoking appears to be a risk factor for wheezy illness but not for atopy. This finding was confirmed when these data were analyzed for the subgroup of infants with definite allergy. None of the environmental risk factors were significant for this group of infants.

We combined data for S-E classes 1, 2, and 3 because the number for classes 1 and 2 was small and they were similar in manner. Classes 4 and 5 were also combined for the same reason. There was an independent effect of S-E class on asthmatic symptoms. It was probably an indirect effect through bad housing conditions, such as dampness and crowding with increase risk of transmissible respiratory infections. Other studies have found a relationship between S-E class and wheezing during infancy.^{16, 23}

There was a trend for respiratory symptoms to be more prevalent in infants born in summer months, but no significant independent effect could be demonstrated on either asthmatic symptoms or skin test sensitivity to grass pollen or HDM. Morrison Smith and Springett⁷ found a higher risk of asthma and positive skin reactions to HDM for infants born in summer months. The cause of this relationship remains unclear. Virus infections are more common in winter; therefore, this cannot explain an increased incidence of respiratory symptoms. Exposure to birch pollen in the first few months of life was believed to increase the risk of birch-pollen allergy.²⁴ Further studies are needed to clarify the association between month of birth and allergic sensitization.

Environmental factors play an important role in the prevalence of recurrent wheezing but not other allergic disorders in the first year of life. Exposure to some environmental factors in early life may be important in increasing the risk of sensitization. Unfortunately, there appears to be a clustering of avoidable risk factors. Mothers who formula-fed their babies tended to smoke and more often belonged to lower S-E groups. It is important to educate mothers, especially mothers belonging to lower S-E groups, to breast-feed and avoid smoking.

We thank health visitors and midwives of the Isle of Wight Health Authority for their help and cooperation. Mrs. Fiona Lampe, Statistical Department, Southampton University, for help with statistical analysis, and the Isle of Wight Health Authority Trustees and Wessex Medical Trust for their generous support.

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